Open, Non-controlled Clinical Studies to Assess the Efficacy and Safety of a Medical Device in Form of Gel Topically and Intravaginally Used in Postmenopausal Women with Genital Atrophy

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Summary

Menopause is often associated with vaginal atrophy and related symptoms, such as vaginal dryness, burning, itching, and dyspareunia, decrease in libido and in general a decrease in the quality of life. The common treatment up to the 1990's has been the oral hormone replacement therapy (HRT), but this treatment has been consequently re-considered due to its adverse effects. Topical estrogenic products have been subsequently developed to minimize the systemic adverse effects of the oral HRT, but they are still considered at risk in case of prolonged use. As an alternative, two clinical trials were performed to investigate the effects of a medical device in the form of a gel, containing hyaluronic acid, liposomes, phytoestrogens from *Humulus lupulus* extract, and Vitamin E, with the aim of testing its safety and efficacy in post-menopausal women with urogenital atrophy. The first pilot study confirmed in 10 women the good safety profile, both locally and systemically, of the device applied on the external genitals at the dose of 1–2 g/day for 30 days. The second study was carried out, according to a multicenter, open, non-controlled design, in 100 post-menopausal women assigned to the vaginal application of 2.5 g of gel/day for 1 week followed by two applications/week for 11 weeks. The primary end-point was the evaluation of vaginal dryness assessed by a Visual Analogue Scale both by the investigator and the subject. Secondary end-points were the evaluation of all other symptoms and signs associated with atrophic vaginitis (itching, burning, dyspareunia, vaginal inflammation/oedema and rash assessed by a 4-point scale and presence of vaginal abrasions and disepithelialisation), and the recording of adverse events during the study.

At the end of the treatment, an overall judgment on the efficacy and safety of the device was made by the investigator and a judgment on the acceptability of the treatment was made by the subjects.

The results showed a marked effect of the tested product on the vaginal dryness and on all other symptoms and signs with statistically significant reductions since the first week of treatment. No treatment-related adverse events were complained by the subjects and the treatment course showed a high level of acceptability by the subjects. This device could be considered an effective and safe alternative treatment of genital atrophy in post-menopausal women, especially when HRT is not recommended.

Key words

- Gynaecological drugs
- *Humulus lupulus*
- Hyaluronic acid
- Medical device
- Menopause
- Phytoestrogens
- Vaginal atrophy
- Vaginal dryness

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Zusammenfassung

Offene, nicht kontrollierte klinische Studien zur Untersuchung der Wirksamkeit und Sicherheit eines Präparats in Form eines Gels zur topischen intravaginalen Anwendung bei postmenopausalen Frauen mit Genitalatrophie

In der Menopause treten häufig vaginale Atrophien und damit verbundene Symptome wie vaginale Trockenheit, Brennen, Jucken, Dyspareunie, Libido-Störungen und allgemein eine Verminderung der Lebensqualität auf. Bis zu den 1990er Jahren wurde üblicherweise mit einer oralen Hormonersatztherapie (HRT) behandelt, diese wurde dann jedoch wegen ihrer Nebenwirkungen neu überdacht. In der Folge wurden topische Östrogen-Präparate entwickelt, um die systemischen Nebenwirkungen der oralen Hormonersatztherapie zu minimieren, doch auch bei diesen wird vermutet, daß bei längerfristiger Anwendung ein Risiko besteht. Daher wurden zwei klinische Studien mit einem Alternativpräparat in Form eines Gels durchgeführt, das Hyaluronsäure, Liposomen, Phytoöstrogene aus *Humulus lupulus*-Extrakt und Vitamin E enthält, um die Sicherheit und Wirksamkeit bei postmenopausalen Frauen mit Urogenitalatrophie zu untersuchen. Die erste Pilotstudie mit 10 Frauen bestätigte das gute Sicherheitsprofil des Präparats – sowohl lokal als auch systemisch – bei Anwendung an den äußeren Genitalien in einer Dosierung von 1–2 g pro Tag 30 Tage lang. In der zweiten Studie, die nach einem offenen, nicht kontrollierten Multicenter-Design durchgeführt wurde, wurden 100 postmenopausale Frauen mit vaginal appliziertem Gel behandelt, und zwar mit 2,5 g pro Tag 1 Woche lang, gefolgt von 2 Applikationen pro Woche 11 Wochen lang. Der primäre Endpunkt war die Untersuchung der vaginalen Trockenheit, die sowohl vom Prüfarzt als auch von der Probandin anhand einer visuellen Analogskala vorgenommen wurde. Die sekundären Endpunkte waren die Untersuchung aller anderen Symptome und Zeichen, die mit einer atrophischen Vaginitis einhergehen (Jucken, Brennen, Dyspareunie, vaginale Entzündungen/Ödeme und Exantheme – untersucht anhand einer 4-Punkte-Skala – sowie vaginale Abrasionen und Disepithelialisation) und die Aufzeichnung von unerwünschten Ereignissen während der Studie.

Am Ende der Therapie wurde vom Prüfarzt eine Gesamtbeurteilung der Wirksamkeit und Sicherheit des Präparats und von den Probandinnen eine Beurteilung der Akzeptabilität der Therapie vorgenommen.

Die Ergebnisse zeigten eine ausgeprägte Wirkung des getesteten Präparats auf die vaginale Trockenheit sowie alle anderen Symptome und Zeichen; diese wurden ab der ersten Woche der Behandlung statistisch signifikant reduziert. Von den Probandinnen wurden keine therapieabhängigen unerwünschten Ereignisse festgestellt, und die Akzeptabilität der Therapie wurde von ihnen als sehr hoch eingestuft. Das Präparat kann als wirksame und sichere Alternativtherapie für Genitalatrophie bei postmenopausalen Frauen betrachtet werden, insbesondere wenn eine orale Hormonersatztherapie nicht empfohlen wird.

1. Introduction

Menopause is associated with a marked reduction in endogenous estrogen production. Low levels of circulating blood estrogens have different deleterious effects, including those on the lower genito-urinary tract [1, 2]. The vaginal epithelium becomes atrophic and dry, and this condition can cause vaginal discomfort, itching and dyspareunia. The thinned endometrium and the increased vaginal pH level, induced by estrogens deficiency, predispose the vagina to infections and mechanical weakness [3]. Moreover, a reduced vaginal secretion causes problems during sexual intercourse, leading to the onset of a drop in libido [4]. Because atrophic vaginitis is attributable to estrogens deficiency, it may occur also in premenopausal women, who take antiestrogenic medications or who have medical or surgical conditions that result in decreased levels of estrogens.

These symptoms of urogenital ageing cause considerable discomfort and consequently an obvious reduction in the quality of life of women, who are affected by. Furthermore, the number of women presenting with menopause-related urogenital complaints is expected to increase in the future due to a longer life expectancy [5].

Systemic and topical HRT have been frequently used in the late 1990's for treating the symptoms of postmenopausal woman, including vulvar and vaginal atrophy. The woman health initiative (WHI) trial in 2002 and other studies published since 2002 fundamentally changed our understanding of risk-benefit ratio associated with HRT [2, 6]. These new recommendations are subject of controversy and raise new problems for practitioners. Therefore, there will be a growing need of new safe and effective forms of treatment for genital atrophy in post-menopausal women.

Vaginal moisturizers and lubricants may be beneficial in the treatment of women with atrophic vaginitis. Vaginal moisturizers provide both short- and long-term relief by changing the fluid content of endothelium. Vaginal lubricants provide only short-term relief. Women with contraindications to estrogens or hormone replacement therapy could use lubricants for intercourse-related dryness or moisturizers for more continuous relief.

The results of two open, non-controlled clinical trials with the use of a medical device in the form of a vaginal gel are reported. The ingredients were hyaluronic acid, liposomes, Vitamin E, and phytoestrogens contained in *Humulus lupulus* extract, and it has been used either by topical or intravaginal route in women with genital atrophy. No placebo group was included in the studies due to ethical reasons and because the use of a vehicle as intravaginal placebo might have altered clinical outcomes (e.g. change of vaginal pH, and/or local epithelial changes when applied to the vagina) [7].

Hyaluronic acid sodium salt is a high molecular weight substance which belongs to the group of glycosaminoglycans and consists of repetitive disaccharide units (glucuronic acid and N-acetylglucosamine). Hyal-

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uronic acid is able to store extremely large water quantities, and on the skin it forms a moisturizing, viscoelastic, non sticky, air- and light-permeable and thus invisible film. Hyaluronic acid optimised the water balance, whereby the skin becomes smooth and more elastic [8]. Moreover, hyaluronic acid plays an important role in maintaining tissue integrity, as well as in facilitating the migration of cells during inflammation and wound repair.

The medical device is in form of a gel with a liposomal structure formulated as moisturizer and lubricant to increase softness and elasticity of the vaginal mucous membrane.

Humulus lupulus is a member of the hemp family, which has grown wild since ancient times in Europe, Asia and North America. Modern herbal medicine practitioners use hops as free radical scavengers, as well as for its endocrine properties. Scientific studies have detected a range of phytoestrogens with different biological activities, so suggesting a potential role of hops in women's health [9–11]. Vitamin E, a fat-soluble vitamin, is an antioxidant involved in the metabolism of all cells. It protects vitamin A and essential fatty acids from oxidation in the body cells and prevents breakdown of body tissues.

2. Materials and methods

2.1. Medical device description

The medical device[1)] is a non-hormonal vaginal gel with a liposomal structure formulated as moisturizer and lubricant. The gel contains the following active ingredients: extract from *Humulus lupulus*, hyaluronic acid, liposomes formed by cholesterol and lecithin. Other ingredients include jellifying agents, preservatives and water.

The product contains 1 % of a mother tincture hop extract. The method of preparation is standardized as follows: The plant used grow wild in a restricted area of northern Italy, namely Colli Erganei (Monselice), Padova. The fresh strobili are collected in a restricted period of time each year (i.e. 10 days) during the female inflorescence in September. They are immediately put in the process of hydro-alcoholic maceration (ratio 1:10), this is by strictly following the French pharmacopoeia. Under this condition, there is no variability due to climate, geographic area and/or season.

Liposome formation is granted by a technology done by the sponsoring company. Presence of monolaminar liposomes, multilaminar liposomes, multivescicular liposomes has been confirmed by scan microscopy (freeze fracture) during the product production of the released batch and at the end of the shelf life of the device.

2.2. Pilot study

The study was conducted according to the GCP and the principles deriving from the Helsinki declaration after obtaining the approval by the Ethical committee of the Policlinico San Matteo of Pavia and the written informed consent by each patient included in the study.

Ten postmenopausal women with symptoms and signs of urogenital atrophy, aged between 45 and 70 years, were considered as eligible for the study. Patients with vaginal infections due to *Neisseria gonorrheae, Trichomonas vaginalis* and *Chlamydia* were excluded.

The study has been planned as a single centre, open, not controlled pilot study to assess the local and systemic safety of the tested product in the treatment of postmenopausal urogenital atrophy. The patients were treated with the study product used at a single daily dose of 1–2 g for 30 days. The product had to be applied on the vulvar region once daily in the evening before going to bed.

The primary endpoint was to assess the local and systemic safety of the product, through the monitoring of adverse events, vital signs and laboratory testing. Secondary objectives were the following: assessment of urogenital symptoms (pruritus and burning); assessment of urogenital signs (erythema, oedema and vaginal discharge); global assessment on the safety as performed both by the investigator and patient.

Two visits were scheduled during the study, the first at baseline (Visit t0) and the second one at the end of the study (Visit t30). During the two visits the following efficacy assessments were performed: vulvovaginal signs (oedema, erythema, vaginal discharge, genital atrophy) according to the following semi-quantitative ordinal four-point scale: 1 = absent; 2 = mild; 3 = moderate; 4 = severe. Daily assessment of urogenital symptoms (pruritus and burning) using the above mentioned scale, was performed by the subject and reported on the patient's diary.

Safety was assessed by means of vital signs and routine laboratory tests.

Any adverse event observed by the investigator and/or reported by the subject was recorded according to the international standard.

The final judgement of subject and investigator on the safety of the study product was performed by using a three point scale (1 = poor, 2 = good, 3 = very good).

2.3. Core study

Written informed consent was obtained from each patient before starting the study, the protocol was approved by the Ethical Committee of the Scassi Hospital, Genoa (Italy) and by the Ethical Committee of the Medical University Hospital, Pavshih Kommunarov pr. 79 Donetsk (Ukraine). The study was conducted according to the GCP and the principles deriving from the Helsinki declaration. The study was conducted according to a multicenter, open, non-controlled design.

Overall, 100 women, aged between 45 and 65 years, with surgical menopause or physiological menopause from at least 1 year, and presenting with vaginal dryness and related symptoms, were considered as eligible for the study. Exclusion criteria were: expectancy of non-compliance; genital anomalies; positive Pap test result in the last 3 months; genital infection (confirmed by microbiological evaluation); vulvo-vaginal contact allergies; vaginal medication administered within 15 days prior to the inclusion in the trial and during the study; history of alcohol and drug abuse; participation in other clinical trial during the last month before enrolment.

The device has been used as follows: one application per day deeply into the vagina, at bedtime, by means of an applicator dosed at 2.5 g of gel, for a period of seven consecutive days followed by two applications per week of 2.5 g of gel for 11 weeks.

[1)] Manufacturer: Polichem SA, Lugano (Switzerland). Brands/distributors: Gynomunal Vaginalgel®, Taurus Pharma GmbH, Bad Homburg (Germany); Esvegyne®, Thèramex Italia S.p.a., Segrate, Mi (Italy).

Five visits were performed during the 3-month period of the study: at baseline, 8 days after the beginning of the application, and then after 28, 56, and 84 days.

At baseline visit, the investigator assessed the subjects for eligibility according to the stated inclusion/exclusion criteria and collected demographic information, medical and gynecological history and current medical status of the women. A Pap test was done, if negative results in the past 3 months were not available, as well as a microbiological examination of vaginal smear and urine.

Few days after the baseline visit, when the vaginal tampon and urine culture results have been obtained, the subject was asked to attend the investigational site, and in case of negative culture the patient was included in the trial and the medical device was delivered.

At each visit a gynecological examination was performed including examination of vulva, vagina, cervix, ovary, uterus, tube; objective vaginal symptoms (inflammation, edema, presence of vulvovaginal abrasions, presence of disepithelialization of the vaginal mucosa), subjective vaginal symptoms (vaginal dryness, itching, burning, dyspareunia).

The severity of symptom "vaginal dryness" (primary endpoint of the study) was evaluated on the basis of a Visual Analogue Scale ranging from 0 (no feeling of dryness) to 10 (maximum, intolerable feeling of dry vagina). This scale was filled in by the investigator in the case report form (CRF) during the visits and by the patient in the diary.

Other symptoms and signs were assessed by the investigator through a 4-point scale (1 = absent; 2 = mild; 3 = moderate; 4 = severe), except for abrasions and disepithelialisation assessed as present or absent.

Moreover, each patient recorded on the diary, always by a four-point scale (1 = absent; 2 = mild; 3 = moderate; 4 = severe), the symptoms (itching, burning, dyspareunia) daily for all the treatment period.

2.4. Statistical analysis

2.4.1. Pilot study

The incidence of symptoms, signs and adverse events (i.e. number of patients with one or more symptoms, signs and adverse events) and their 95 % confidence limits have been reported. Severity of symptoms and signs of laboratory variables have been analysed descriptively. Deviations from reference range of laboratory test have been assessed.

The significance of final-baseline differences for signs and symptoms was assessed both by ranks and by frequencies comparison.

2.4.2. Core study

The statistical analyses were performed by SAS (Version 8). The data of all subjects who completed the study according to the protocol (PP population) were included in the statistical analysis. Descriptive statistics were performed for each variable. The primary variable (vaginal dryness) was analysed by Repeated Measures Analysis of Variance, single-factor repeated measures to explore trends in the different times, and Paired Samples t-tests to examine differences between scores at various points in time. Inferential analysis of secondary variables (ordinal data) was made by Friedman test.

3. Results

3.1. Pilot study

Ten post-menopausal Caucasian women, aged between 45 and 70 years (mean age 54.7 ± 7 years), average height 161 ± 4.4 cm, average weight 51 ± 8.8 kg, were enrolled in this study and all completed the trial procedures, without any deviation from the protocol. Therefore no one was excluded from the analyses performed.

With regard to the laboratory tests most subjects showed results within the reference range for all examined parameters at the two visits; only few subjects had values outside the reference range at the final examination, but in the investigator's opinion only one of these results had to be considered clinically significant. It concerned a "slight increase" in monocyte count at the final visit of 13.2 % (upper limit of normal range: 9 %). However, in the opinion of the investigator there was no relationship with the treatment nor any countermeasure was necessary.

None of the subjects enrolled in this trial experienced any adverse event during the period of observation of the trial.

The medical evaluation performed at the final visit revealed the presence of the same frequency and distribution of the pathological condition identified at the beginning of the trial (one case of osteoporosis and three cases of depression).

The results of the statistical analysis on signs and symptoms, by considering the differences between baseline and end-of-treatment data, are reported in Table 1.

All symptoms and signs markedly reduced or disappeared at the end of treatment. The analysis showed a statistically significant ($p < 0.05$) decrease of the symptoms pruritus and burning at the end of treatment compared to baseline values, while for all other parameters no statistically significant differences were seen, prob-

Table 1: Sign/symptom severity in 10 postmenopausal women applied the test product for 30 days.

	Vulvovaginal signs/symptoms											
	Redness		Oedema		Vaginal discharge		Itching*		Burning*		Genital atrophy	
	t0	t30	t0	t30	t0	t30	t0	t30	t0	t30	t0	t30
Absent	7	10	8	10	6	8	2	6	1	6	9	10
Mild	3	–	2	–	2	1	2	2	1	2	–	–
Moderate	–	–	–	–	2	1	2	2	5	1	1	
Severe	–		–	–	–	–	4	–	3	1	–	–
Totals	10	10	10	10	10	10	10	10	10	10	10	10

* $p < 0.05$ (comparison by ranks and by frequencies).

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Table 2: Core study female subject characteristics.

Subjects	n
Included	100
Married	69
With children	64
Age	54 (min 48, max 63)
Body mass index	25 (min 17.7, max 39.26)

ably due to the small number of subjects included in this pilot study.

3.2. Core study

Overall 108 Caucasian women were screened for entering in the study; eight women did not comply with the inclusion criteria, finally 100 women aged between 48 and 63 years (mean age 54.6 ± 10.7) were enrolled and assigned to the treatment according to the study protocol, the subjects' characteristics are summarized in Table 2.

Fourteen subjects prematurely discontinued the study, three subjects for lack of compliance, two for consent withdrawal, and nine were lost to follow-up. Overall 86 subjects completed the study (PP population).

The severity of vaginal dryness (primary endpoint), measured by means of the VAS, decreased in the PP population from 78.36 at baseline to 58.57 at Visit 1 (8 days), to 32.82 at Visit 2 (28 days), to 7.37 at Visit 3 (56 days) and to 0.0 at Visit 4 (84 days). The difference at the ANOVA was highly significant ($F = 1031.3$; $p < 0.001$). Multiple comparison confirmed a significant decrease vs. baseline starting from the 1st study time point, namely at Visit 1 after 8 days of treatment. The results obtained for vaginal dryness are summarised in Fig. 1.

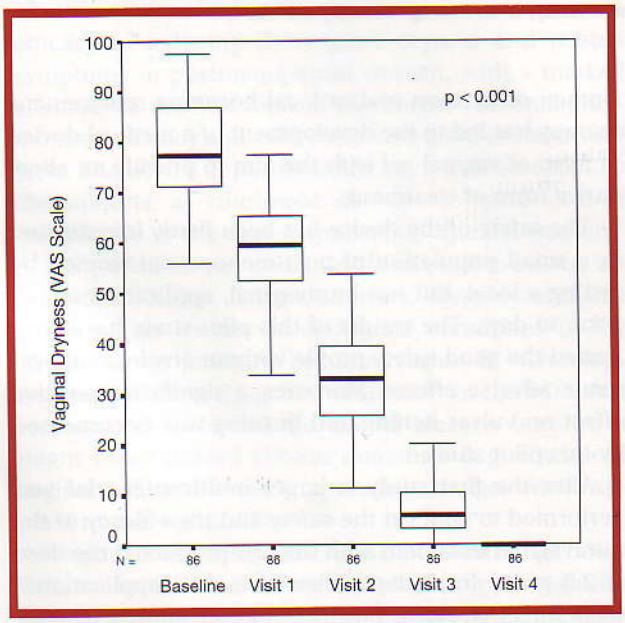

Fig. 1: Vaginal dryness (visual analogue scale) by visit in postmenopausal women treated with the test product for 12 weeks (Visit 1 = 8 days; Visit 2 = 28 days; Visit 3 = 56 days; Visit 4 = 84 days).

The results of the evaluation of the subjective parameters, itching, burning and dyspareunia, in the PP population are reported below.

At baseline visit, itching was present as severe symptom in 70 women and as moderate in 16 women; the symptom progressively disappeared and only 2 women complained of mild itching at the end of treatment (Visit 4). The data are detailed in Fig. 2A. The average severity of itching, measured by the 4-point scale, decreased from 4.94 at baseline to 3.98 at Visit 1, to 3.05 at Visit 2, to 1.56 at Visit 3 and to 1.47 at Visit 4 ($p < 0.001$). Data are summarized in Fig. 2B.

At the baseline visit, burning was severe in 50 women, moderate in 24 women and mild in 12 women; the symptom progressively reduced in intensity or disappeared and at the end of treatment only 2 women complained of mild burning. The data are detailed in Fig. 2A. The average severity of burning, measured by the 4-point scale, decreased from 4.90 at baseline to 3.72 at Visit 1, to 3.09 at Visit 2, to 1.67 at Visit 3 and to 1.62 at Visit 4 ($p < 0.001$). Data are summarized in Fig. 2C.

Dyspareunia was present as severe symptom in 12 women, as moderate in 52 women and as mild in 22 women at the baseline; the symptom progressively disappeared and only 1 woman complained of mild dyspareunia at the end of treatment (Visit 4). The data are detailed in Fig. 2A. The average severity of dyspareunia, measured by the 4-point scale, decreased from 4,81 at baseline to 3.67 at Visit 1, to 2.93 at Visit 2, to 1.87 at Visit 3 and to 1.72 at Visit 4 ($p < 0.001$). Data are summarized in Fig. 2D.

Inflammation/oedema of the vaginal mucosa, initially severe in 24 women, moderate in 31 women, mild in 20 women and absent in 11 women at baseline, progressively disappeared in most subjects and only 4 women complained of mild inflammation/oedema of the vaginal mucosa at the end of treatment (Visit 4). The average severity of the symptom, measured by the 4-point scale, decreased from 4.64 at baseline to 3.56 at Visit 1, to 2.90 at Visit 2, to 1.98 at Visit 3 and to 1.91 at Visit 4 ($p < 0.001$). Data are summarized in Fig. 3A.

Rash of the vaginal mucosa was present as severe symptom in 18 women, as moderate in 27 women, as mild in 33 women and was absent in 8 women at baseline; the symptom progressively disappeared in all women at the end of treatment. The average severity of rash decreased from 4.66 at baseline to 3.56 at Visit 1, to 2.78 at Visit 2, to 2.02 at Visit 3 and to 1.96 at Visit 4 ($p < 0.001$). Data are summarized in Fig. 3B.

Disepithelialization of the vaginal mucosa was present in 22 % of the women at the baseline visit. The symptom progressively disappeared in all these women at the end of the treatment. Data are summarized in Fig. 3C. Vulvovaginal abrasions of the mucosa were present in 20 % of the women at the baseline visit. The symptom progressively disappeared in all these women at the end of the treatment. Data are summarised in Fig. 3D.

The compliance to the treatment was complete in 84 subjects and partial in 2. Data are summarized in Fig. 4A.

A

		Itching	Burning	Dyspareunia
Baseline	absent	0	0	0
	mild	0	12	22
	moderate	16	24	52
	severe	70	50	12
Visit 1	absent	0	10	18
	mild	13	29	35
	moderate	69	45	32
	severe	4	2	1
Visit 2	absent	0	12	28
	mild	82	70	54
	moderate	4	4	4
	severe	0	0	0
Visit 3	absent	79	80	77
	mild	6	6	9
	moderate	1	0	0
	severe	0	0	0
Visit 4	absent	84	84	85
	mild	2	2	1
	moderate	0	0	0
	severe	0	0	0

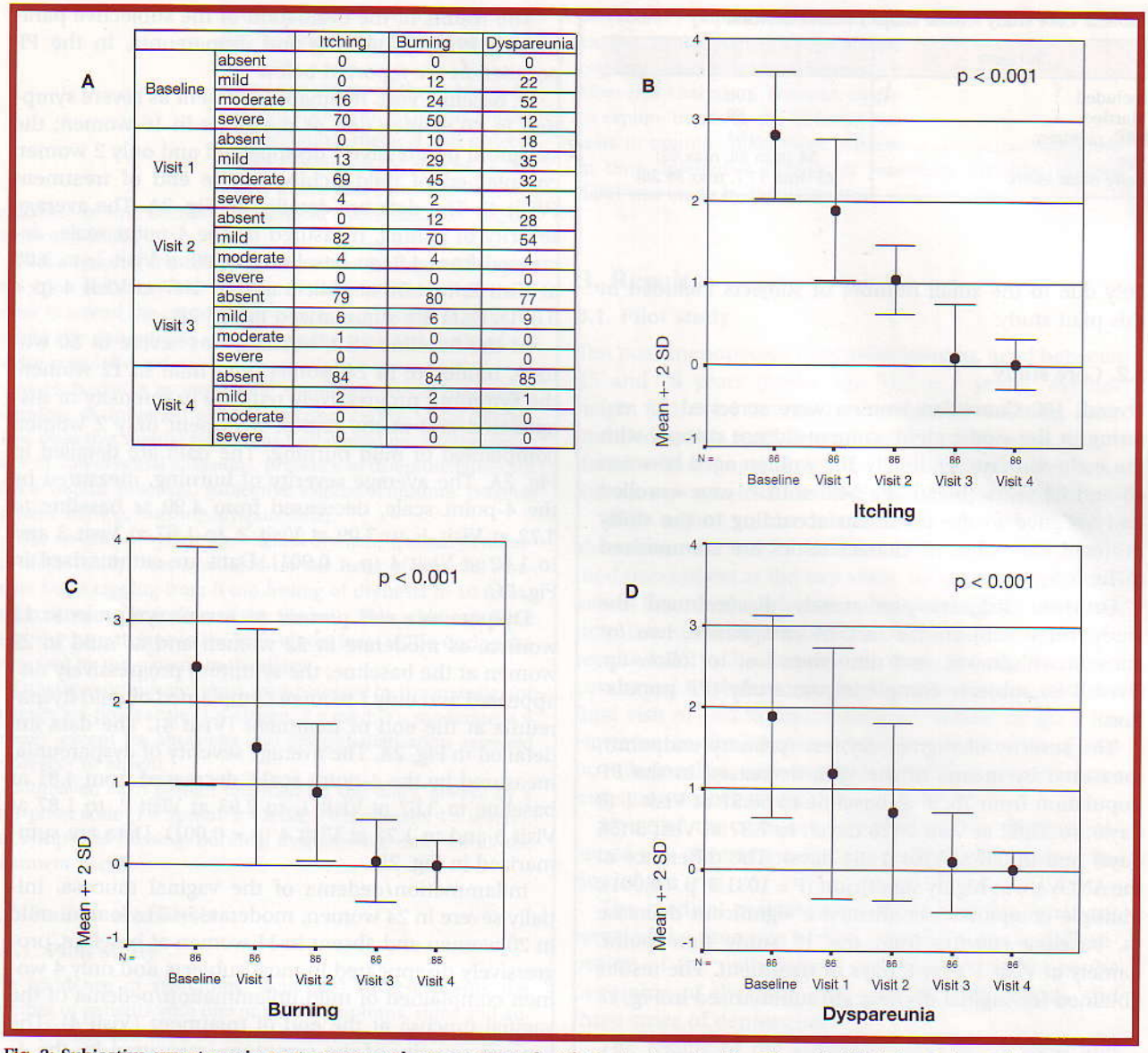

Fig. 2: Subjective symptoms in postmenopausal women treated with the test product for 12 weeks (Visit 1 = 8 days; Visit 2 = 28 days; Visit 3 = 56 days; Visit 4 = 84 days) A: number of patients by symptom severity; B–D: average severity ± 2 SD.

The overall judgment on the efficacy of the study product, as assessed by the investigator, was optimal in 70 subjects, good in 15 subjects and moderate in 1 subject. Data are summarized in Fig. 4B.

The safety was defined by the investigator as optimal in 83 subjects, good in 2 subjects and sufficient in 1 subject. Data are summarized in Fig. 4C.

The acceptability of the device by the subjects was defined as decidedly acceptable by 73 subjects, easily acceptable by 12 subjects and acceptable by 1 subject. Data are summarized in Fig. 4D. Two subjects complained of mild and transient rhinitis and one patient complained of mild rhinitis and throat pain during the study; all these events recovered, and they were not considered as related to the study treatment.

4. Discussion

The growing need of new safe and effective forms of treatment for uro-genital atrophy in post-menopausal women other than oral or local hormone replacement therapy has led to the development of a medical device in form of vaginal gel with the aim to provide an alternative form of treatment.

The safety of the device has been firstly investigated in a small population of post-menopausal women by testing a local, but not intravaginal, application of 1–2 g for 30 days. The results of this pilot study have confirmed the good safety profile without any local or systemic adverse effects. Moreover, a significant positive effect on vulvar itching and burning was documented by this pilot study.

After the first study, a larger multicenter trial was performed to confirm the safety and the efficacy of the intravaginal treatment with the test product at the dose of 2.5 g/day for 7 days followed by two applications/week for 11 weeks in postmenopausal women. The results confirmed the favourable safety profile of the device even after a prolonged period of treatment and its

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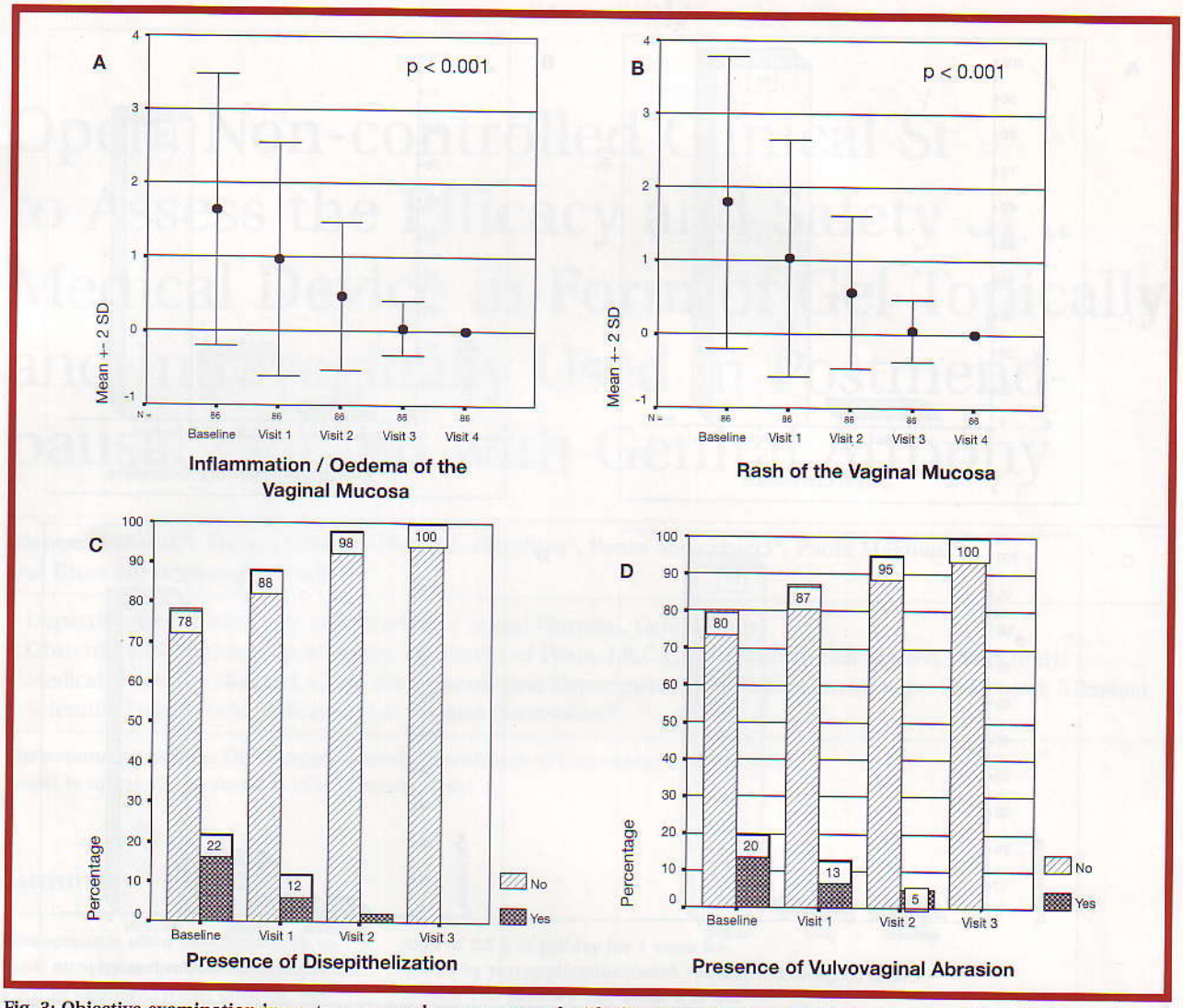

Fig. 3: Objective examination in postmenopausal women treated with the test product for 12 weeks (Visit 1 = 8 days; Visit 2 = 28 days; Visit 3 = 56 days; Visit 4 = 84 days) A–B: average severity ± 2 SD. C–D: number of patients by symptom presence.

efficacy in reducing the vaginal dryness and related symptoms in postmenopausal women, with a marked effect since the first week of treatment. The final judgment on efficacy and safety was very good in most subjects. The device application has been well accepted by the subjects, as confirmed also by the good level of compliance to the device application in most women.

No guideline was available about studies on the reported indication. On the contrary, the only available guideline on treatment of vaginal conditions is the "Guidance for industry. Bacterial vaginosis – Developing antimicrobial drugs for treatment" of the FDA that recommends to avoid the use of placebo because it might cause altered clinical outcomes (e.g. change of vaginal pH, and/or local epithelial changes when applied to the vagina) [7].

Vaginal moisturizers and lubricants seem to be beneficial in the treatment of women with atrophic vaginitis. Vaginal moisturizers provide both short- and long-term relief by changing the fluid content of endothelium. Vaginal lubricants provide only short-term relief.

The positive results in the treatment of vaginal atrophy obtained in these studies are due to the formulation of the tested product, that contains ingredients (hyaluronic acid, liposome, phytoestrogens contained in *Humulus lupulus*, and Vitamin E) that allow to slow down the natural ageing process of the vaginal area by enhancing its natural moisture and maintaining the vaginal and vulvar tone and firmness. The efficacy of the medical device's respective components shall be investigated separately in future.

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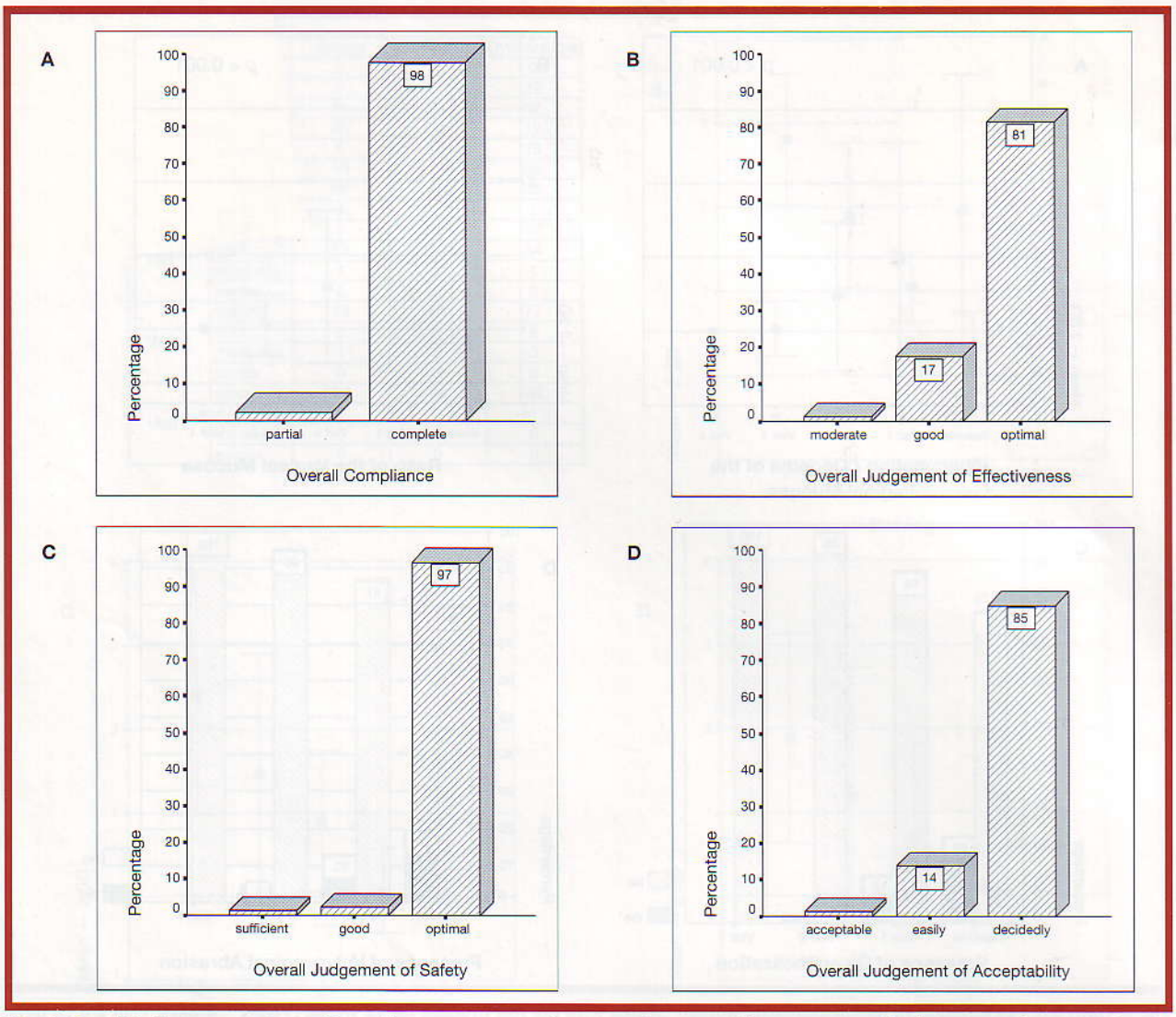

Fig. 4: Overall judgement and compliance in postmenopausal women after 3 months treatment with the test product (A–C: by the investigator, D: by the subject).

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